ATTY. DKT. NO. 215233.00400
CUSTOMER NO. 27160

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Kenneth W. Locke et al. Examiner: Oh, Taylor V.

Serial No.: 10/601,861

Art Unit: 1625

Filed: June 24, 2003

For: Process for making polymorphic form A of 4-[6-acetyl-3-[3-(4-acetyl-3-hydroxy-2-propylphenylthio)propoxy]-2-propylphenoxy]butyric acid

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
Washington, DC 20231

Sir:

I, Kenneth W. Locke, Ph.D., hereby make the following declaration:

1. I received a Ph.D. degree in Pharmacology from the Emory University School of Medicine in the year 1985.

2. I have 20 years of experience in the pharmaceutical industry focused primarily on drug discovery and the preclinical and early clinical development of novel therapeutics. Each of the positions described below has provided me with the skills, experience and insight to identify promising drug candidates. My career in the pharmaceutical industry began at Hoechst-Roussel Pharmaceuticals, Inc.,

heading laboratories for analgesics and anti-inflammatory, and later Alzheimer's disease, drug research. In 1989, I joined Interneuron Pharmaceuticals, Inc., as Manager, Behavioral Neuroscience, taking on positions of increasing responsibility over the next 11 years. Before leaving Interneuron, as Executive Director, Preclinical Development, I was responsible for all aspects of preclinical development for the company's drug portfolio, as well as for in-licensing candidate evaluation. In 2000, I joined Tanabe Research Laboratories U.S.A., Inc., as Vice President of Research, to coordinate the research efforts of chemists and biologists in identifying novel drug development candidates. I am currently employed by MediciNova, Inc., the assignee of the above-referenced patent application, with offices located at 4350 La Jolla Village Drive - Suite 950, San Diego, CA 92122. My current title is Senior Vice President, Portfolio Management.

3. I am named as a co-inventor of the invention claimed in the above-referenced patent application. I have read the contents of the Final Office Action mailed May 19, 2005. I have also been apprised of the Examiner's request, made to assignee's counsel on August 30, 2005, to provide this declaration directed to the superior solubility properties of the claimed orthorhombic crystals of 4-[6-acetyl-3-[3-(4-acetyl-3-hydroxy-2-propylphenylthio)propoxy]-2-propylphenoxy]butyric acid (also referred to in the specification of the above-referenced patent application as Form A), as well as the results of certain experiments that are described in Appendix A, attached hereto.

4. As described in the specification of the above-referenced patent application, for example, at page 9, Example 4, the claimed method provides orthorhombic crystals (Form A) that exhibit physical characteristics which are

PAGE 3/5 * RCVD AT 9/20/2005 11:44:28 AM [Eastern Daylight Time] * SVR:WAS-US-FAX-01/6 * DNIS:8292 * CSID: * DURATION (mm-ss):02-10
PAGE 3/5 * RCVD AT 9/20/2005 12:09:19 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-6/30 * DNIS:2730689 * CSID: * DURATION (mm-ss):01-38

different from those displayed by undesired monoclinic crystals. For instance, the desired orthorhombic crystals displayed greater and unexpected solubility compared with the undesired monoclinic crystals of Form B. For example, at 30 °C the solubility of Form B was calculated to be 6.1 g/L, while that of Form A was calculated to be 15.7 g/L – that is, at 30 °C, the claimed orthorhombic crystals displayed more than twice the solubility of the undesired monoclinic crystals. This physical characteristic of greater solubility is also observed at 22 °C and at 40 °C.

5. I would also like to draw the Examiner's attention to Figures 6 and 7 of Appendix A, attached hereto. These figures depict powder x-ray diffraction (PXRD) analyses of tablets made from the claimed orthorhombic crystals and the undesired monoclinic crystals, respectively. As can be readily seen from these figures, the crystalline structure of the two forms, Form A and Form B, are retained in the manufacture of the respective tablets. It is therefore reasonable to assume that the greater solubility characteristics of the claimed orthorhombic crystals are retained in the tablets, which in turn would offer a benefit of greater solubility/bioavailability of active drug to a patient.[1]

6. Other aspects of the Appendix A, which are noteworthy, are Figures 2 and 5. Figure 2 depicts the PXRD analyses for the claimed orthorhombic crystals (Form A) versus undesired monoclinic crystals (Form B or Form C). Note, for example, the three singlet peaks for Form A between about 11.5 and 16.0 (2-Theta scale), whereas Forms B and C (both monoclinic) exhibit three doublet peaks in the same region. Figure 5 depicts differential scanning calorimetry (DSC) thermograms

[1] Dissolution experiments using tablets made from different polymorphic forms of 4-[6-acetyl-3-[3-(4-acetyl-3-hydroxy-2-propylphenylthio)propoxy]-2-propylphenoxy]butyric acid were inconclusive because tablets were manufactured with widely different particle sizes for the two polymorphic forms. The particle size used for the manufacture of a tablet

PAGE 4/5 * RCVD AT 9/20/2005 11:44:28 AM [Eastern Daylight Time] * SVR:WAS-US-FAX-01/6 * DNIS:8292 * CSID: * DURATION (mm-ss):02-10
PAGE 4/5 * RCVD AT 9/20/2005 12:09:19 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-6/30 * DNIS:2730689 * CSID: * DURATION (mm-ss):01-38

of Forms A versus B (including tablets made from the two forms). As can be seen from Figure 5, the phase transition for Form A crystals occurs at a lower temperature than Form B crystals. It may be inferred from these results that Form B is the thermodynamically favored crystal structure for this compound.

7. In summary, the claimed method provides orthorhombic crystals which have been shown to exhibit distinct physical and chemical characteristics from the undesired monoclinic forms, including a greater solubility relative to undesired monoclinic crystals.

8. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity or enforceability of any patent maturing from the above-referenced patent application.

Dated: 9/20/05

By: _____

Kenneth W. Locke, PH.D.

from Form A was more than four times the particle size for the manufacture of a tablet from Form B. The dissolution profile of the tablets tested are depicted in Figure 4 of Appendix A, attached hereto.

PAGE 5/5 * RCVD AT 9/20/2005 11:44:28 AM [Eastern Daylight Time] * SVR:WAS-US-FAX-01/6 * DNIS:8292 * CSID: * DURATION (mm-ss):02-10
PAGE 5/5 * RCVD AT 9/20/2005 12:09:19 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-6/30 * DNIS:2730689 * CSID: * DURATION (mm-ss):01-38

A Study of Different Polymorphic Forms of a New Drug Substance, MN-001

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OBJECTIVE

- Identify NCE MN-001 API polymorphic forms
- Develop dissolution test method with discriminating power using four prototypes of 250 mg tablets
- Evaluate the impact of batch-to-batch differences in polymorphic forms and powder particle sizes of API on the dissolution behavior of MN-001 250 mg tablets
- Investigate stability of the polymorphic forms of MN-001 within the tablets

INTRODUCTION

- MN-001 is a new chemical entity with six known polymorphic forms and low intrinsic solubility in water. The chemical structure is shown in figure 1
- A 250mg strength tablet has been developed and is currently being tested in clinical trials. Different prototypes of 250 mg tablets using polymorphic form A of API were developed using various formulation processes.
- A dissolution testing method has been developed. A leading formulation was selected based on stability results, such as impurity profile and dissolution rate.
- A number of batches of API with various particle sizes and polymorphic forms have been used for manufacturing tablets.
- The impact of batch-to-batch differences in polymorphic forms and powder particle sizes of API on the dissolution behavior of MN-001 250 mg tablets as well as the nature of the polymorphic forms of MN-001 within the tablets were investigated.

METHODOLOGY

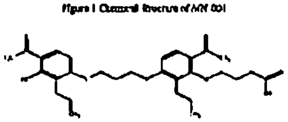
Dissolution

The dissolution method was developed and validated using USP apparatus II at 75 rpm and 900mL of 1% Tween 80 in phosphate buffer at pH 7.5 as dissolution medium. The dissolution profile was determined with sampling time points at 10, 20, 30, 45, 60 minutes at 75 rpm and then additional 15 min at 250 rpm with 10 mL medium replacement. Samples were determined by UV at [illegible] nm.

PXRD

Siemens D5000 Diffractometer System Operating at 40kV/30mA. A high power line focus Cu Kα-source was used combined with a solid state Kevex detector. The experimental data were collected in step scan mode (at 0.02°, 1 s) within the range of 2.5°–40° (2theta). The obtained data were processed by Diffrac plus[TM] Software.

Figure 1 Chemical Structure of MN 001



RESULTS AND DISCUSSION

Polymorphic forms of API

- A total of six known polymorphic forms of MN-001 API have been identified.
- Three polymorphic forms of API have been observed in batches made in current API manufacturing site as per figure 2.
- Different polymorphic forms of MN-001 are formed under specific reaction conditions. Form A and B have been optimized.

Evaluation of Dissolution method

- Four prototypes of MN-001 tablets with API polymorphic form A were developed.
- The dissolution testing method was developed to discriminate between the dissolution profiles of prototype of tablets.
- The dissolution method was successfully used to evaluate the dissolution profile for various prototype formulations as per figure 3
- A leading formulation (MDNF1500701) was selected based on stability results, such as impurity profile and dissolution rate.

The effect of polymorphic forms of API on dissolution profile of MN-001 tablets

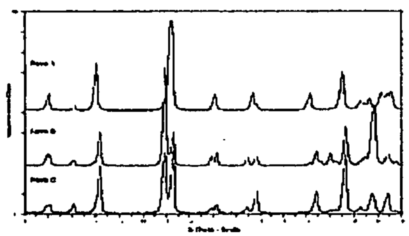
- The dissolution profiles of two batches of MN-001 tablets with two different major polymorphic forms A and B of API are shown in figure 4.
- A faster release (more than 90% in 10 minutes) in tablets with API form B was found compared with that using API form A. Since particle size of form A API (31% > 425μm) was different from that of form B API (90% < 100μm), it was not clear whether the faster release was due to API polymorphic form, particle size or form changed during tablet manufacturing process.

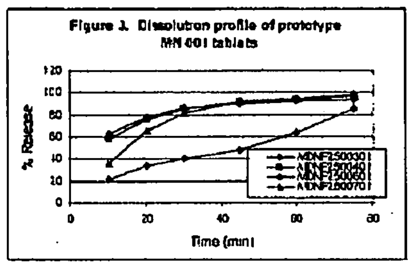
Evaluation of polymorphic form of MN-001 within tablets

- The batch-to-batch API, granule & tablets were analyzed by DSC and PXRD.
- DSC thermograms of both forms of API were similar as shown in figure 5. So this analytical technique was not used any further.
- PXRD analysis showed that a different polymorph form B of the API had been synthesized instead of the expected form A.

- Figures 6 and 7 show PXRD of tablets lot MDNF1500701 with Form A of API and tablets Lot MDNF1500702 with form B of API, respectively. These show no evidence of form changes during tablet manufacturing process.
- The PXRD of placebo is shown in figure 8. The placebo peaks labeled as "p" in PXRD of active tablet show very limited contribution due to high drug load at 50%.

Figure 2 PXRD of Three Main Polymorphic Forms of MN-001 API





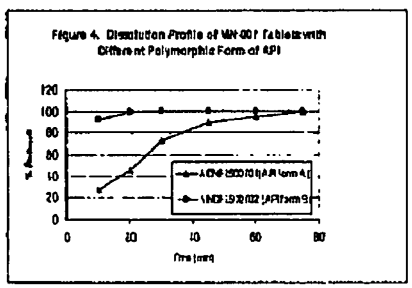


Figure 5 DSC Thermograms of MN-001 API and tablets

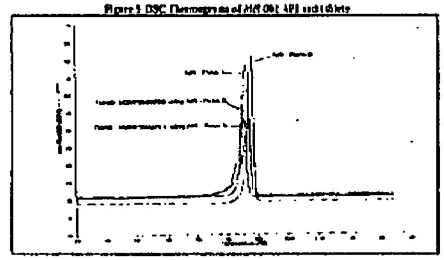


Figure 6 PXRD of MN-001 Form A API and subsequent tablets lot MDNF1500701

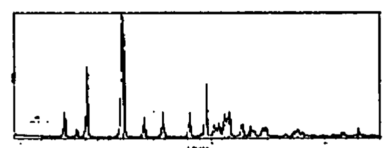


Figure 7 PXRD of MN-001 Form B API, granule and tablets lot MDNF1500702

Figure 7 Cont'd

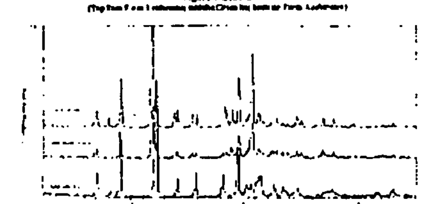
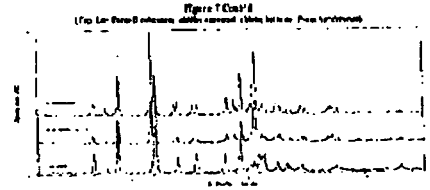
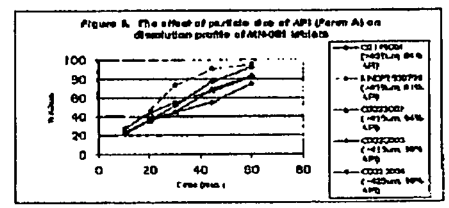


Figure 7 Cont'd





The effect of particle size of API (form A) on dissolution profile of MN-001 tablets

- Tablets were manufactured using different lots of API with different particle size particle size ranges as follows: range I with about 90% of API particle size < 425μm and range II with about 99% of API particle size > 425μm. The dissolution profiles were showed in figure 8.
- It was concluded that API particle size affects behavior of dissolution rate since batch size and formulation process is same except different API. The release rate of MN-001 in tablets was decreased with increase of particle size. At least 91% of release in MN-001 tablets using API with particle size range I was observed compared with 71–77% release using API with particle size range II.

CONCLUSIONS

- The dissolution method was successfully used to evaluate the dissolution profile of tablets with different formula, particle size and polymorphic forms of API.
- PXRD analysis showed that a different polymorph of the API than previous batches had been synthesized and that no polymorphic structural changes or transitions had occurred due to the formulation process.
- The effect of particle size of API for form A of API on the behavior of dissolution profile was observed. The larger particle size of API with form A is cause of slow release of tablets.
- It is unclear whether the very rapid release for MN-001 tablets manufactured using polymorphic form B of API can be attributed to smaller particle size or to the nature of polymorphic form B, or both. The effect of API particle size using polymorphic form B on dissolution profile of tablets is subjected to further investigation.
- Therefore, polymorphic form and particle size should be carefully considered in the formulation of MN-001